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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/981,583	02/03/98	DICKMANNS A	028622/0/0

HM12/0217

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EXAMINER	
HARRIS, A	
ART UNIT	**PAPER NUMBER**
1642	15

DATE MAILED: 02/17/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trad marks

Office Action Summary

Application No.	Applicant(s)
08/981,583	Dickmanns et al.
Examiner	**Group Art Unit**
Alana M. Harris, Ph. D.	1642

☒ Responsive to communication(s) filed on *Nov 22, 1999*

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claim

☒ Claim(s) *1-22 and 29-37* is/are pending in the applicat

Of the above, claim(s) *13-15, 32, 36, and 37* is/are withdrawn from consideration

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-12, 16-22, 29-31, and 33-35* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☒ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☒ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). *3-5.* (filed March 11, March 24 & March 31, 1998, respectively).

☐ Interview Summary, PTO-413

☒ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

1. Applicant's election with traverse of Group I (claims 1-12, 16-22, 29-31, 33 and 34) in Paper No.14 (filed November 22, 1999) is acknowledged. Upon reconsideration Group III (claim 35), drawn to a method of treating by administering a pharmaceutical composition comprising the epithelial tumor cell will be rejoined with Group I.

The argument that Groups I-VI are not independent and distinct inventions is not found persuasive for the reasons set forth in the restriction requirement (Paper No. 5, mailed August 27, 1999). As to the question of burden of search, the claims of Groups I-VI are classified differently, necessitating different searches in the U.S. Patent shoes. Further, classification of subject matter is merely one indication of the burdensome nature of the search involved. The literature search, particularly relevant in this art, is not co-extensive and is much more important in evaluating the burden of search. Clearly different searches and issues are involved in the examination of each group. For these reasons the remainder of the restriction requirement is deemed to be proper and is adhered to.

The requirement is therefore made FINAL. Further, Groups IV-VI involve various method steps, which require additional searching.

However, the policies set forth in the Commissioner's Notice of February 28, 1996 published on March 26, 1996 at 1184 O.G. 86 will be followed. Method claims limited to the scope of the allowable product claims will be rejoined and examined at the time the product claims are indicated as being allowable.

2. Claims 23-28 have been cancelled.

Claims 29-37 have been added.

Claims 1, 3-9, 11-16, 18 and 20-22 have been amended.

Claims 1-22 and 29-37 are pending.

Claims 13-15, 32, 36 and 37, drawn to non-elected inventions are withdrawn from examination.

Claims 1-12, 16-22, 29-31 and 33-35 are examined on the merits.

Priority

3. This application, filed under former 37 CFR 1.60 lacks the necessary reference to prior application. A statement reading "This application claims priority to International Application PCT/EP96/02474, filed 6/24/96 and Foreign Application (European) 95109860.7, filed 6/23/95 should be entered following the title of the invention or as the first sentence of the specification.

Applicant is reminded that in order for a patent issuing on the instant application to obtain the benefit of priority under 35 U.S.C. 119(a)-(d), a claim for such foreign priority must be made in this application.

Drawings

4. The drawings are objected to because of reasons cited on attached form PTO 948 completed by draftsman. Correction is required.

Specification

5. The disclosure is objected to because of the following informalities: the brief description of the figures lack a separate brief description: Figure 4a, Figure 4b, Figure 4c, Figure 5a and Figure 5b.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 33-35 are rejected under 35 U.S.C. 112, first paragraph, because the specification, does not reasonably provide enablement commensurate with the scope of the claimed invention. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

a. Claims 33-35 are broadly drawn to "a pharmaceutical composition comprising the epithelial tumor cell". The specification while being enabling for a composition comprising an epithelial tumor cell of claim 1 and a pharmaceutically acceptable carrier, does not reasonably provide enablement for a "pharmaceutical composition" comprising these same components. Claims drawn to "pharmaceutical compositions" are broadly interpreted to read on compositions

effective for use as *in vivo* human therapeutics. The epithelial tumor cell of the invention is completely uncharacterized structurally and functionally. The mere fact that the cell is epithelial in nature is not sufficient to establish a role in the applicability as a pharmaceutical or diagnostic composition. Epithelial cells could be derived from a number of organ systems, for example breast, bronchial and tracheal epithelium, as well from the gastrointestinal tract. In the absence of an established role of an epithelial tumor cell from a specific organ system the role of a composition comprising any or all epithelial tumor cells it would be impossible to predict the utility and the therapeutic effect of the administration of any epithelial tumor cell for the treatment of cancer and/or metastasis of cancer. The selection and development of such human therapeutics is art known to be highly unpredictable. The specification exemplifies no examples of the effective use of the effective use of the epithelial tumor cell as a pharmacological agent and no such uses are art known. The specification does not list from which organ this claimed therapeutic epithelial tumor cell would be obtained. This reasonably conjures the question as to how effective in the would the application of a composition comprising a non-specified organ epithelial tumor cell would be. Therefore, due to the unpredictability of therapeutics and the absence of any evidence concerning the effectiveness of the claimed pharmaceutical composition as a pharmacological agent, the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use with a reasonable expectation of success, the invention commensurate in scope with this claim. The applicant is advised to amend the claim to delete the first recitation of "pharmaceutical".

8. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claims 7, 12, 29 and 33-35 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a. The recitation "replication deficiency" in claim 7 is vague and indefinite. What actually constitutes a deficiency in the replication process?

b. The recitation "said replication deficiency" in claim 7 lacks proper antecedent bases in claim 6. Appropriate correction is required.

c. The recitation "B7" in claim 12 is vague and indefinite. This terminology is not art known. Applicant is advised to recite the proper and full terminology.

d. Claim 33 is not proper in the recitation "or an antibody molecule selected from the group consisting of an antibody, a fragment of said antibody, a derivative of said antibody or a fragment of said derivative, wherein said antibody molecule specifically recognizes said epithelial tumor cell." Claim 33 is examined is examined only to the extent that it read on a pharmaceutical composition comprising epithelial tumor cells. Applicant is advised to delete the said recitation.

Claim Rejections - 35 USC § 102

10. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

11. Claims 1-3, 6-10, 16-19, 21 and 22 are rejected under 35 U.S.C. 102(b) as being anticipated by Garcia et al. (Molecular and Cellular Biology 6(6):1974-1982), see whole document. Garcia et al. disclose an autologous, disseminated immortalized rabbit mammary epithelial tumor cell with metastatic potential which has integrated in its genome or another replicative genetic element the DNA encoding the early region (large T antigen) of non-infectious SV40 DNA, claims 1-3, 6 and 8. The epithelial tumor cell contains at least one defect in the origin of replication, claim 7.

Garcia et al. also disclose that the epithelial tumor cell has integrated in its genome at least one additional oncogene, wherein additional oncogene is c-Ha-ras, the same as that claimed (claims 9 and 10). The *in vitro* process by which the tumor cell incorporated the DNA encoding at least one immortalizing oncogene into a non-immortalized epithelial tumor cell with metastatic potential is disclosed by Garcia et al., claim 16. The step of incorporating DNA comprised microinjection, which was performed after the step of carrying out a primary expansion of said

non-immortalized epithelial tumor cells, claims 17 and 18. The primary expansion comprised the step of culturing in a medium comprising epidermal growth factor on the extracellular matrix, collagen coated tissue flasks, the same as that claimed (claims 19, 21 and 22).

Claim Rejections - 35 USC § 103

12. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

13. Claims 1, 4, 5 and 16-20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Garcia et al.(Molecular and Cellular Biology 6(6):1974-1982), in view of Schlimok et al. and Yanagihara et al. The teachings of Garcia et al. of an immortalized epithelial tumor cell with metastatic potential have been discussed in the paragraphs above. Garcia et al. do not teach the epithelial tumor cell according to claim 1 which is a human non-immortalized tumor cell derived from body fluid such as bone marrow.

However, Schlimok et al. do teach the detection of human epithelial tumor cell in bone marrow aspirates. It would have been *prima facia* obvious to one of ordinary skill in the art at the time the claimed invention was made to readily obtain disseminated non-immortalized human epithelial tumor cells derived from body fluid, specifically bone marrow aspirates. One of

ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by teachings in Garcia et al. and Schlimok et al. that the specified tumor cells could be obtained with the use of monoclonal antibodies directed against the cytokeratin polypeptide #18 specifically expressed in cells derived from epithelia to detect the claimed tumor cells in bone marrow aspirates.

Furthermore, Yanagihara et al. teach the introduction of an oncogene into a cell to elucidate the role of oncogenes in the metastatic process. One of ordinary skill in the art would have been motivated to introduce an oncogene into the cell line to monitor the metastatic ability of the oncogene-bearing cells. Such cells would provide a useful system for understanding the mechanisms by which oncogenes influence the occurrence of metastasis. And the detection process of Schlimok et al. of such tumor cells would allow clinicians to monitor and recognize cancer status, thus establish the most useful and efficient diagnostic therapies effective to patients.

14. Claims 1, 11, 12, 16, 29 and 30 are rejected under 35 U.S.C. 103(a) as being unpatentable over Garcia et al.(Molecular and Cellular Biology 6(6):1974-1982), in view of Blankenstein et al. (Current Biology 3:694-698, 1991). The teachings of Garcia et al. of an immortalized epithelial tumor cell with metastatic potential have been discussed in the paragraphs above. Garcia et al. do not teach the epithelial tumor cell according to claim 1 having integrated in its genome or another replicative genetic element an externally introduced gene encoding a cytokine immunostimulatory factor, such as interleukin-4 (IL-4).

However, Blankenstein et al. teach the transfer of single cytokine genes into cancer cells. It would have been *prima facia* obvious to one of ordinary skill in the art at the time of the claimed invention was made to introduce genes encoding cytokine immunostimulatory factors, such as IL-4, granulocyte colony-stimulating factor and tumor necrosis factor into the tumor cell of Garcia et al. One of ordinary sill in the art would have been motivated to do so with a reasonable expectation of success by the teachings well known in the art, that the transfer and the expression of such immunostimulatory factor genes into cancer cells would mediate powerful tumor suppression potential in T-cell deficient animals and appear to be effective even for poorly or non-antigenic tumors. Additionally, Blankenstein et al. report that "cancer cells transfected to produce certain cytokines might induce effective tumor-specific immunity in cancer patients".

15. Claims 1, 16-19, 21 and 31 are rejected under 35 U.S.C. 103(a) as being unpatentable over Garcia et al.(Molecular and Cellular Biology 6(6):1974-1982), in view of Sigma Cell Culture Catalogue and Price List (1995).The teachings of Garcia et al. of production of a cultured immortalized epithelial tumor cell in a medium comprising epidermal growth factor (EGF) have been discussed in the paragraphs above. Garcia et al. do not teach a medium comprising recombinant human epidermal growth factor (rhEGF) or the basic fibroblast growth factor (bFGF), recombinant human basic fibroblast growth factor (rhbFGF).

However, the Sigma Cell Culture Catalogue teaches the availability of these growth factor supplements at the time the claimed invention was made. It would have been *prima facia* obvious

to one of ordinary skill in the art at the time the claimed invention was made to use rhEGF and rhbFGF to supplement the culture medium. One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by teachings in Garcia et al. and the Sigma Cell Culture Catalogue to order these supplements and use them in view of the recommended concentrations and practices listed in the technical section of the catalogue.

16. Claims 1, 33 and 34 are rejected under 35 U.S.C. 103(a) as being unpatentable over Garcia et al.(Molecular and Cellular Biology 6(6):1974-1982), in view of Gottlinger et al. (Int. J. Cancer 38:47-53, 1986). The teachings of Garcia et al. of an immortalized epithelial tumor cell with metastatic potential have been discussed in the paragraphs above. Garcia et al. do not teach a composition comprising the epithelial tumor cell according to claim 1, nor the said composition comprising a vaccine in combination with a vaccine adjuvant.

However, Gottlinger et al. teach compositions containing epithelial cell surface antigens and *Bordetella pertussis* adjuvant suitable for mounting an immunological response. It would have been *prima facia* obvious to one of ordinary skill in the art at the time the claimed invention was made to manufacture a composition comprising the epithelial tumor cell of claim 1 in combination with a *B. pertussis* adjuvant. One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by teachings of Garcia et al. and Gottlinger et al. that the production of an adjuvant prepared by culturing autologous epithelial tumor cells coupled with *B. pertussis* adjuvant would be suitable for administration to a non-

human animal for augmenting immune responses in order to generate antibodies that would allow one skilled in the art to biochemically characterize a specific antigen defined by the generated antibodies.

17. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Alana M. Harris whose telephone number is (703) 306-5880. The examiner can normally be reached on Monday through Friday from 7:30 am to 4:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Paula Hutzell, can be reached on (703) 308-4310. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Alana M. Harris, Ph.D.
Patent Examiner, Group 1642
February 14, 2000

PAULA K. HUTZELL
SUPERVISORY PATENT EXAMINER